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EXAMINER
RAMIREZ, DELIA M

ART UNIT	PAPER NUMBER
1652	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/606,129	Applicant(s) MAINES, MAHIN D.	
	Examiner Delia M. Ramirez	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-67* is/are pending in the application.

4a) Of the above claim(s) *10-67* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 June 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

Claims 1-67 are pending.

Applicant's election with traverse of Group I, claims 1-9 drawn to a method for regulating protein kinase activity with the biliverdin reductase of SEQ ID NO: 1, 3, 18, 19, 34 or 35, in Paper No. 9, filed on 1/4/2002 is acknowledged.

Applicant's traverse is on the ground(s) that the claims of the instant application are closely related and therefore, require common areas of search. Also, Applicants argue that since Groups I-XI have been classified under class 435, subclass 25, there is only one class/subclass to search, therefore no serious burden to the Office is imposed.

Applicant's arguments have been fully considered but are not found persuasive. The instant application contains claims to 11 patentably distinct methods of use for the biliverdin reductase of SEQ ID NO: 1, 3, 18, 19, 34 or 35 which have analytical as well as therapeutical applications. In addition, the instant application contains claims to the biliverdin reductase of SEQ ID NO: 1, 3, 18, 19, 34 or 35, DNA encoding the biliverdin reductase of SEQ ID NO: 1, 3, 18, 19, 34 or 35, and antibodies against the biliverdin reductase of SEQ ID NO: 1, 3, 18, 19, 34 or 35. While it is true that publications containing polynucleotide (Group XIII) information such as open reading frame sequences typically disclose the corresponding polypeptide (Group XII), it is false to assume that the only source of information about a polypeptide is one in which polynucleotide information is disclosed. Similarly, one cannot expect publications containing polypeptide information to disclose information on antibodies (XIV) or methods of use (I-XI). In regard to the classification of Groups I-XI, it should be noted that a comprehensive search in

an application involves more than just a class/subclass search. Therefore, examination of all the groups in the instant application would require searching for polynucleotides, polypeptides, antibodies, 11 methods of use, and class/subclass searches for all these patentably distinct inventions.

The requirement is deemed proper and therefore is made FINAL.

Claims 10-67 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Drawings

1. The drawings have been reviewed and are objected under 37 CFR 1.84 or 1.152. See attached Notice of Draftsperson's Patent Drawing Review. Applicant is required to submit the drawing corrections within the time period set in the attached Office communication. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in ABANDOMENT of the application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 1 (claims 2-9 dependent thereon) is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. There is no step indicating how one can determine if regulation of protein kinase activity has taken place.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is directed to a method of regulating protein kinase activity of any protein kinase with any biliverdin reductase, or fragment or variant thereof. The specification discloses that human/rat biliverdin reductase has kinase activity in addition to reductase activity (page 4, lines 1-5). The specification indicates that it appears that human/rat biliverdin reductase has serine/threonine/tyrosine kinase activity (page 28, lines 13-14; page 72, lines 19-21). The kinase activity of human/rat biliverdin reductase was discovered from examination of the primary structure, which indicated that a consensus sequence present in all kinases was also present in human/rat biliverdin reductase (page 2, lines 19-27). The specification also discloses that the activity of human protein kinase C (PKC) can be stimulated by contacting PKC with biliverdin reductase (page 71, lines 4-21), PKC can be stimulated by the polypeptide of SEQ ID NO: 34, and PKC can be inhibited by the polypeptide of SEQ ID NO: 19 (page 71, lines 22-33).

However, there is no information on how a biliverdin reductase, or fragment or variant thereof, not containing the kinase consensus sequence can regulate any protein kinase. A

fragment of the human biliverdin reductase of SEQ ID NO: 3 is 100% sequence identical to a fragment of the tRNA(pro) from black pine chloroplasts (Tsudzuki et al., SPTREMBL accession number Q32948, November 1996). Also, since not all protein kinases are expected to be phosphorylated by biliverdin reductase, one would require some information as to which protein kinases can be regulated with the claimed method. Applicant's disclosure has not provided information as to which protein kinases can be regulated with the claimed method, with the exception of PKC. No working examples are provided which show regulation of tyrosine protein kinases with biliverdin reductases comprising kinase activity either. The specification only discloses a method of regulating PKC with the human biliverdin reductase of SEQ ID NO: 1 or 3 and the polypeptides of SEQ ID NO: 19 or 34, which is insufficient to put one of ordinary skill in the art in possession of the attributes and features of methods of regulating any protein kinase with any biliverdin reductase, or fragments or variants thereof. Thus, one skilled in the art cannot reasonably conclude that Applicant had possession of the claimed invention at the time the instant application was filed.

4. Claim 1 (claims 2-5 and 7-9 dependent thereon) are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for regulating protein kinase activity of human protein kinase C (PKC) with (1) the human biliverdin reductase of SEQ ID NO: 1 or 3, and (2) the polypeptides of SEQ ID NO: 19 or 34, does not reasonably provide enablement for a method for regulating protein kinase activity of <u>any protein kinase</u> with <u>any biliverdin reductase, or fragment or variant thereof</u>. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The criteria for undue experimentation, summarized in *re Wands*, 8, USPQ2nd 1400 (Fed. Cir. 1988) are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims.

Claim 1 is directed to a method of regulating any protein kinase with any biliverdin reductase, or fragment or variant thereof. The scope of the claim is not commensurate with the enablement provided in regard to the large number of protein kinases and biliverdin reductases (fragments or variants thereof) encompassed by the method claimed. The specification discloses a method of regulating one human protein kinase (PKC), which is a serine/threonine kinase, with the biliverdin reductase of SEQ ID NO: 1 or 3 and the polypeptides of SEQ ID NO: 19 or 34, all of which have kinase activity. As discussed previously, no examples are provided which indicate that tyrosine protein kinases can be regulated by a biliverdin reductase with kinase activity or examples of protein kinases being regulated by biliverdin reductases lacking the kinase function. Since protein kinases are part of a large family of enzymes with different characteristics, substrates and specificities, it is not expected that all protein kinases will be regulated by biliverdin reductases.

The current state of the art (Salim et al., J. Biol. Chem. 276:10929-10934, 2001) in regard to human biliverdin reductases indicates that human biliverdin reductase is most likely to be a serine/threonine phosphoprotein (page 10933, column 1, last paragraph, lines 1-4). The

teachings of Salim et al. appear to be in conflict with Applicant's assertion that human/rat biliverdin reductase is a serine/threonine/tyrosine phosphoprotein (page 28, lines 13-14; page 72, lines 19-21). If human biliverdin reductase does not have tyrosine kinase activity, it is not clear that human or rat biliverdin reductase can be used in a method to regulate tyrosine protein kinases. Therefore, due to the lack of relevant examples, the amount of information provided, the lack of knowledge about which protein kinases can be regulated by biliverdin reductase, and the unpredictability of the prior art in regard to the type of kinase activity present in biliverdin reductase (human as well as other species), one of ordinary skill in the art would have to go through the burden of undue experimentation in order to determine (1) which protein kinases can be regulated by biliverdin reductase and (2) which biliverdin reductases, or fragments or variants thereof, can be used to regulate protein kinases. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to use the invention in a manner reasonably correlated with the scope of the claims.

5. Claim 8 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 8 is directed to a method of regulating protein kinase activity comprising contacting any protein kinase with any biliverdin reductase, or fragments or variants thereof, in any cell *in vivo*. The specification discloses that human/rat biliverdin reductase has kinase activity in addition to reductase activity (page 4, lines 1-5). The specification indicates that it

appears that human/rat biliverdin reductase has serine/threonine/tyrosine kinase activity (page 28, lines 13-14; page 72, lines 19-21). The kinase activity of human/rat biliverdin reductase was discovered from examination of the primary structure, which indicated that a consensus sequence present in all kinases was also present in human/rat biliverdin reductase (page 2, lines 19-27). The specification also discloses that the activity of human protein kinase C (PKC) can be stimulated *in vitro* by contacting PKC with biliverdin reductase (page 71, lines 4-21), PKC can be stimulated by the polypeptide of SEQ ID NO: 34, and PKC can be inhibited by the polypeptide of SEQ ID NO: 19 (page 71, lines 22-33).

However, there is no information as to how one can regulate protein kinase activity of any protein kinase with any biliverdin reductase *in vivo*. The standard definition for "in vivo" in the art is "within the living body" (Dorland's Illustrated Medical Dictionary, 29th Edition, W. B. Saunders, 2000). Applicant's disclosure has not provided any guidance as to how one can detect regulation of protein kinase activity with biliverdin reductase *in vivo*. Also as discussed previously, no information has been disclosed on how to regulate a protein kinase with biliverdin reductases lacking the kinase consensus sequence. No information has been provided as to how one can regulate and target specific protein kinases *in vivo*. Since not all protein kinases are expected to be phosphorylated by biliverdin reductase, it is not clear how one can regulate any protein kinase *in vivo* without any guidance as to determining which protein kinases are being regulated. Applicant's disclosure has not provided information as to which protein kinases can be regulated with the claimed method, with the exception of PKC *in vitro* only. No working examples are provided which show regulation of tyrosine protein kinases with biliverdin reductases comprising kinase activity either. The specification only discloses a method of

regulating PKC with human biliverdin reductase and the polypeptides of SEQ ID NO: 19 and 34 *in vitro*, which is insufficient to put one of ordinary skill in the art in possession of the attributes and features of methods of regulating any protein kinase with any biliverdin reductase, or fragments or variants thereof *in vivo*. Thus, one skilled in the art cannot reasonably conclude that Applicant had possession of the claimed invention at the time the instant application was filed.

6. Claim 8 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of regulating protein kinase activity with the biliverdin reductase of SEQ ID NO: 1 or 3 or with the polypeptides of SEQ ID NO: 18, 19, 34, or 35 *in vitro*, does not reasonably provide enablement for a method of regulating protein kinase activity with the biliverdin reductase of SEQ ID NO: 1 or 3 or with the polypeptides of SEQ ID NO: 18, 19, 34, or 35 *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The criteria for undue experimentation, summarized in *re Wands*, 8, USPQ2nd 1400 (Fed. Cir. 1988) are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims.

Claim 1 is directed to a method of regulating any protein kinase with any biliverdin reductase, or fragment or variant thereof, wherein the protein kinase and biliverdin reductase are

contacted in a cell *in vivo*. The scope of the claim is not commensurate with the enablement provided in regard to (1) the large number of protein kinases and biliverdin reductases (fragments or variants thereof) encompassed by the method claimed, and (2) the regulation of protein kinases with biliverdin reductase *in vivo*. The specification discloses an *in vitro* method of regulating one human protein kinase (PKC), which is a serine/threonine kinase, with the biliverdin reductase of SEQ ID NO: 1 or 3 (human) and the polypeptides of SEQ ID NO: 19 or 34, all of which have kinase activity. Applicant's disclosure has not provided any guidance as to how one can detect regulation of protein kinase activity with biliverdin reductase *in vivo*. No examples of protein kinases regulated by biliverdin reductases *in vivo* are disclosed. As discussed previously, no examples are provided which indicate that tyrosine protein kinases can be regulated by a biliverdin reductase with kinase activity or examples of protein kinases being regulated by biliverdin reductases lacking the kinase function *in vivo*. Since protein kinases are part of a large family of enzymes with different characteristics, substrates and specificities, it is not expected that all protein kinases will be regulated by biliverdin reductases *in vitro or in vivo*.

As indicated previously, the teachings of Salim et al. appear to be in conflict with Applicant's assertion that human/rat biliverdin reductase is a serine/threonine/tyrosine phosphoprotein (page 28, lines 13-14; page 72, lines 19-21). If human biliverdin reductase does not have tyrosine kinase activity, it is not clear that human or rat biliverdin reductase can be used in a method to regulate tyrosine protein kinases *in vitro or in vivo*. Therefore, due to the lack of relevant examples, the amount of information provided, the lack of knowledge about which protein kinases can be regulated by biliverdin reductase, the lack of knowledge about how to determine if a protein kinase is regulated by a biliverdin reductase *in vivo*, and the

unpredictability of the prior art in regard to the type of kinase activity present in biliverdin reductase (human as well as other species), one of ordinary skill in the art would have to go through the burden of undue experimentation in order to determine (1) which protein kinases can be regulated by biliverdin reductase, (2) which biliverdin reductases, or fragments or variants thereof, can be used to regulate protein kinases, and (3) if regulation of protein kinase activity has occurred *in vivo*. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to use the invention in a manner reasonably correlated with the scope of the claims.

Conclusion

7. No claim is in condition for allowance.

8. Applicants are requested to submit a clean copy of the pending claims (including amendments, if any) in future written communications to aid in the examination of this application.

9. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
March 15, 2002

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